A Facile Synthesis of 8-Arylamino- and 8-Hetarylaminopurines and their 1- and 3-Deaza Analogs

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A general method for the synthesis of 8-arylamino- and 8-(2-benzothiazolylamino)-purines and their 1- and 3-deaza analogs is reported. The need for the presence of the desulfurizing agent in the preparation of the 8-arylamino derivatives is demonstrated and evidence for an intermediate thiourea is provided.

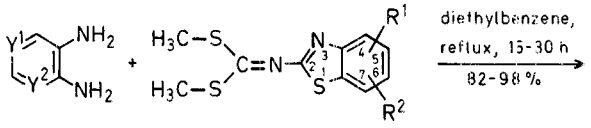
The chemistry of purines and their deaza analogs is an area of major interest in heterocyclic and medicinal chemistry. Consequently, a wealth of synthetic approaches to the purine ring system have been developed[1], most of them making use of imidazoles and 4,5-disubstituted pyrimidines as starting materials, though a few syntheses using acyclic precursors have been reported. Nevertheless, a careful inspection of the literature reveals that there is no general method for the preparation of 8-arylamino- or 8-hetarylaminopurines and their 1- and 3-deaza analogs, since Traube-type syntheses have been performed in only certain cases, mainly to introduce a phenylamino group (using phenyl isocyanate[2], phenylcyanamide[2], and diphenylcarbodiimide[3]) or, very seldom, a hetarylamino moiety[4].

On the other hand, substitution of an 8-chloro or an 8-methylthio group is unsuccessful with aryl-[2] and hetarylamines,

being limited to strongly nucleophilic amines, such a alkylamines[5] or ammonia[6].

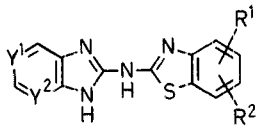
Our experience in the field of dithiocarbamic and dithiocarbonimidic acid derivatives[7,8,9] led us to suppose that their reactions with the appropriate diamines could constitute a general method for the synthesis of the title compounds, since starting products are fairly reactive and easily available.

The procedure used to prepare the 8-(2-benzothiazolylamino)-purines **5** and their 1- and 3-deaza analogs, **6** and **7** – correctly named as imidazo [4,5-*b*]pyridines and imidazo[4,5-*c*]pyridines, respectively – is depicted in Scheme **A**.



1 $Y^1 = Y^2 = N$
2 $Y^1 = CH$, $Y^2 = N$
3 $Y^1 = N$, $Y^2 = CH$

4



5 $Y^1 = Y^2 = N$
6 $Y^1 = CH$, $Y^2 = N$
7 $Y^1 = N$, $Y^2 = CH$

4-7	R^1	R^2
a	H	H
b	6-H_3CO	H
c	4-Cl	H
d	5-H_3C	6-H_3C

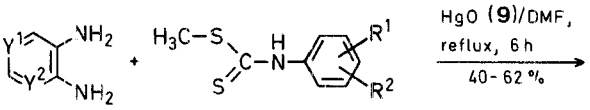
Scheme **A**

The reaction can be conducted in dimethylformamide, but subsequent work-up is unsatisfactory and purification of the final product is laborious. Best results have been obtained in diethylbenzene (isomeric mixture) at reflux temperature, since cooling of the mixture affords the corresponding purine or its deaza analog, which is recovered by filtration in good or nearly quantitative yield (Table 1).

In order to obtain the analogous 8-arylamino derivatives, the reactivity of the corresponding dimethyl *N*-aryldithiocarbonimidates[9] towards the heterocyclic diamines was studied. But, as expected, the lower electrophilicity of these compounds required drastic conditions and the desired products could only be obtained in low yields, together with variable amounts of unidentified byproducts.

To overcome these difficulties, methyl *N*-aryldithiocarbamates were made to react with the *o*-diamino compounds in the presence of red mercury(II) oxide, according to Scheme **B**.

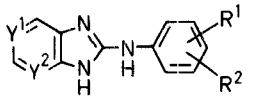
In the case of the 3-deazapurines **12**, the final work-up of the mixture (see experimental procedure below), namely, basification with concentrated ammonium hydroxide must be done twice as, otherwise, the free base is recovered along with its hydrochloride. This fact can be explained by the greater basicity of 3-deazapurines, as compared with those of the corresponding purines and 1-deazapurines (c.f. $pK_a = 6.12$[10], 2.39[5], and 3.5[11], respectively, for the unsubstituted parent rings). Yields range from 40 to 62% (Table 2).



1 $Y^1 = Y^2 = N$
2 $Y^1 = CH$, $Y^2 = N$
3 $Y^1 = N$, $Y^2 = CH$

8

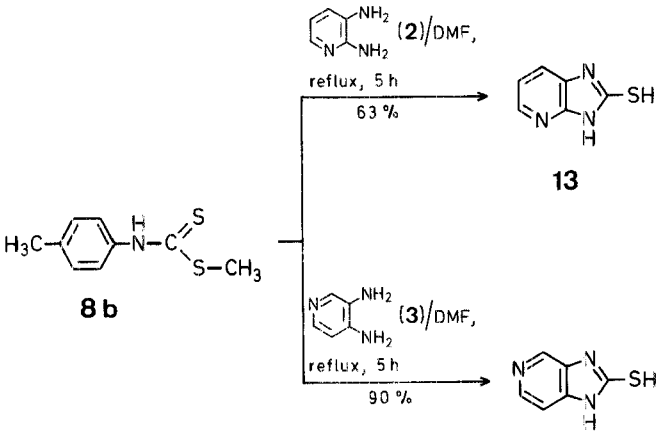
8-12	R^1	R^2
a	H	H
b	4-H_3C	H
c	4-H_3CO	H
d	2-H_3C	4-H_3C
e	3-H_3C	5-H_3C



10 $Y^1 = Y^2 = N$
11 $Y^1 = CH$, $Y^2 = N$
12 $Y^1 = N$, $Y^2 = CH$

Scheme **B**

The presence of the desulfurizing agent **9** is indispensible, for its absence leads to the corresponding 2-mercapto derivatives. Thus, treatment of 2,3-diaminopyridine (**2**) with methyl *N*-(4-methylphenyl)-dithiocarbamate (**8b**) in refluxing dimethylformamide gave 2-mercaptoimidazo[4,5-*b*]pyridine (**13**), identical with an authentic sample synthesized as previously described[12]. Similarly, compound **14**[13] was obtained using 3,4-diaminopyridine (**3**; Scheme C).



8b

13

14

Scheme **C**

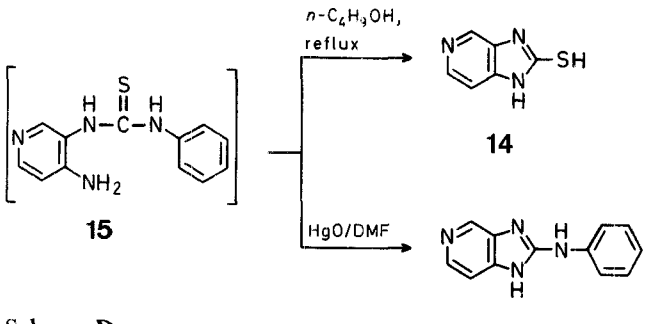
The results summarized in Schemes **B** and **C** can be explained invoking a common intermediate, the corresponding *N*-aryl-*N'*-(3-pyridyl)-thiourea which, however, could not be isolated in the reactions described above.

Nevertheless, the reaction of 3,4-diaminopyridine (**3**) with phenyl isothiocyanate in dioxan at room temperature for 24 h yielded a mixture of two products, the minor one being identified as **14**. Purification of the major product could not be achieved, since on recrystallization a complete conversion to **14** was observed; this fact led us to suppose that structure **15** could be assigned tentatively to the major component of the mixture. The thiourea structure for the unknown compound was confirmed by reaction of the mixture with mercury(II) oxide in refluxing dimethylformamide; this treatment gave 2-phenylaminoimidazo[4,5-*c*]pyridine (**12a**) along with a black precipitate of mercury(II) sulfide, a typical reaction of thioureas that has been exploited in imidazole synthesis[7] (Scheme **D**).

Table 1. 8-(2-Benzothiazolylamino)-purines **5** and 1- and 3-Deazapurines **6** and **7** prepared

Product	Yield [%]	m.p. [°C]	Molecular Formula[a]	M.S. *m/e* (M^+, rel. int.%)	^{1}H-N.M.R. (CF_3COOH/TMS) δ [ppm]
5a	86	> 300	$C_{12}H_8N_6S$ (268.3)	268 (100)	7.9–8.6 (m, 4H); 9.6 (br. s, 2H, H-2, H-6)
5b	82	> 300	$C_{13}H_{10}N_6OS$ (298.3)	[b]	4.1 (s, 3H, OCH_3); 7.4–8.3 (m, 3H); 9.5 (s, 2H, H-2, H-6)
5c	85	> 300	$C_{12}H_7ClN_6S$ (302.7)	[b]	7.6–8.2 (m, 3H); 9.35 (s, 1H, H-6); 9.45 (s, 1H, H-2)
5d	83	> 300	$C_{14}H_{12}N_6S$ (296.3)	[b]	2.6 (s, 6H, $2CH_3$); 7.9 (s, 1H, H-7'); 8.15 (s, 1H, H-4'); 9.5 (br. s, 2H, H-2, H-6)
6a	94	> 300	$C_{13}H_9N_5S$ (267.3)	267 (100)	7.0–8.0 (m, 6H); 8.2 (dd, 1H, J = 5.5 Hz, 1.5 Hz, H-5)[c,d]
6b	98	> 300[e]	$C_{14}H_{11}N_5OS$ (297.3)	297 (74)	3.85 (s, 3H, OCH_3); 6.9–7.7 (m, 4H); 7.8 (dd, 1H, J = 8 Hz, 1.5 Hz, H-7); 8.2 (dd, 1H, J = 5.5 Hz, 1.5 Hz, H-5)[c,d]
6c	97	> 300	$C_{13}H_8ClN_5S$ (301.7)	301 (100)	5.0–8.0 (m, 5H); 8.2 (dd, 1H, J = 5 Hz, 1.5 Hz, H-5)[c,d]
6d	93	> 300	$C_{15}H_{13}N_5S$ (295.3)	295 (100)	2.3 (s, 6H, $2CH_3$); 7.15 (dd, 1H, J = 7.5 Hz, 5 Hz, H-6); 7.35 (s, 1H, H-7'); 7.55 (s, 1H, H-4'); 7.8 (d, 1H, J = 7.5 Hz, H-7); 8.25 (d, 1H, J = 5 Hz, H-5)[c,d]
7a	97	> 300	$C_{13}H_9N_5S$ (267.3)	267 (100)	7.0–8.0 (m, 5H); 8.25 (d, 1H, J = 6 Hz, H-6); 8.8 (s, 1H, H-4); 9.0–10.0 (br. s, 2H, 2NH)[c]
7b	94	> 300	$C_{14}H_{11}N_5OS$ (297.3)	[b]	4.0 (s, 3H, OCH_3); 7.2–7.9 (m, 3H); 8.1 (d, 1H, J = 6 Hz, H-7); 8.5 (d, 1H, J = 6 Hz, H-6); 9.05 (s, 1H, H-4)
7c	98	> 300	$C_{13}H_8ClN_5S$ (301.7)	301 (100)	7.5–8.1 (m, 3H); 8.25 (d, 1H, J = 6.5 Hz, H-7); 8.7 (d, 1H, J = 6.5 Hz, H-6); 9.2 (s, 1H, H-4)
7d	94	> 300	$C_{15}H_{13}N_5S$ (295.3)	295 (100)	2.55 (s, 6H, $2CH_3$); 7.85 (s, 2H); 8.3 (d, 1H, J = 6.5 Hz, H-7); 8.7 (d, 1H, J = 6.5 Hz, H-6); 9.25 (s, 1H, H-4)

[a] Satisfactory microanalyses obtained: C ±0.16, H ±0.14, N ±0.14
[b] No ionization.
[c] In DMSO-d_6.
[d] H-5 and H-7 protons have been assigned by attributing the smallest *ortho*-coupling constant to H-5 (α-position to the nitrogen atom)[14].
[e] Softening from 280 °C.



Scheme **D**

The analogous reaction of 2,3-diaminopyridine (**2**) with phenyl isothiocyanate, under various conditions gave more complex results since, among other products, aniline, *N,N'*-diphenylthiourea, 2-mercaptoimidazo[4,5-*b*]pyridine (**13**), and 2-phenylaminoimidazo[4,5-*b*]pyridine (**11a**) could be identified by comparison with authentic samples.

Melting points were determined using a Büchi 510 apparatus and are uncorrected. ^{1}H-N.M.R. spectra were obtained on a Perkin-Elmer R-12-B spectrometer with TMS as internal reference. Mass spectra were recorded using a Hewlett-Packard 5930-A spectrometer.

8-(2-Benzothiazolylamino)-purines (5), 2-(2-Benzothiazolylamino)-imidazo[4,5-*b*]pyridines (6), and 2-(2-Benzothiazolylamino)-imidazo[4,5-*c*]pyridines (7); General procedure:
A suspension of the corresponding dimethyl *N*-(2-benzothiazolyl)-dithiocarbonimidate **4**[15] (0.002 mol) and the corresponding diamine **1**, **2**, or **3** (0.002 mol) in diethylbenzene (isomeric mixture form EGA-Chemie; 10 ml) is heated under reflux until the evolution of methanethiol ceases (15–30 h). The mixture is cooled, the resulting solid is filtered off, and washed with hexane and acetone to give products **5**, **6**, or **7**, respectively (Table 1).

8-Arylaminopurines (10), 2-Arylaminoimidazo[4,5-*b*]pyridines (11), and 2-Arylaminoimidazo[4,5-*c*]pyridines (12); General Procedure:
To a well stirred suspension of the corresponding diamine **1**, **2**, or **3** (0.003 mol) and red mercury(II) oxide (**9**; 0.65 g, 0.003 mol) in dimethylformamide (6 ml), a solution of the methyl *N*-aryldithiocarbamate **8**[16] (0.003 mol) in dimethylformamide (3 ml) is added dropwise. The mixture is refluxed for 6 h, cooled, and poured into 3% hydrochloric acid (180 ml); the resulting suspension is boiled for 10 min and filtered while hot; the filtrate is made alkaline (pH = 8) with concentrated ammonium hydroxide and the crude product **10** or **11** is isolated by suction, dried and purified by recrystallization (Table 2).

In the case of 2-arylaminoimidazo[4,5-*c*]pyridines **12**, the crude precipitate obtained after basification is poured into concentrated ammonium hydroxide, stirred for 2 h, filtered off, and recrystallized if necessary (Table 2).

2-Mercaptoimidazo[4,5-*b*]pyridine (13):
A solution of 2,3-diaminopyridine (**2**; 0.545 g, 0.005 mol) and methyl *N*-(4-methylphenyl)-dithiocarbamate (**8b**; 0.985 g, 0.005 mol) in dimethylformamide (10 ml) is refluxed for 5 h. The solvent is vacuum-distilled and the resulting solid is recrystallized from ethanol to give **13**, identical with an authentic sample prepared independently[12]; yield: 0.473 g (63%).

2-Mercaptoimidazo[4,5-*c*]pyridine (14):
A mixture of 3,4-diaminopyridine (**3**; 0.327 g, 0.003 mol) and methyl *N*-(4-methylphenyl)-dithiocarbamate (**8b**; 0.591 g, 0.003 mol) in

Table 2. 8-Arylaminopurines **10** and 1- and 3-Deazapurines **11** and **12** prepared

Product	Yield [%]	m.p. [°C] (solvent)	Molecular Formula[a]	M.S. m/e (M^+, rel. int. %)	^{1}H-N.M.R. (CF_3COOH/TMS) δ [ppm]
10a	41	> 300° (DMF/H_2O)	$C_{11}H_9N_5$ (211.2)	211 (100)	7.4–7.9 (m, 5H); 9.15 (s, 1H, H-6); 9.3 (s, 1H, H-2)
10b	57	> 300° (DMF/H_2O)	$C_{12}H_{11}N_5$ (225.2)	225 (100)	2.5 (s, 3H, CH_3); 7.3–7.7 (A_2B_2-system, 4H); 9.2 (s, 1H, H-6); 9.35 (s, 1H, H-2)
10c	41	> 300° (DMF/H_2O)	$C_{12}H_{11}N_5O$ (241.2)	–[b]	4.0 (s, 3H, OCH_3); 7.1–7.6 (A_2B_2-system, 4H); 9.1 (s, 1H, H-6); 9.25 (s, 1H, H-2)
10d	40	278–280° (DMF/H_2O)	$C_{13}H_{13}N_5$ (239.2)	239 (100)	2.3 (s, 3H, CH_3); 2.4 (s, 3H, CH_3); 7.3–7.4 (m, 3H); 9.05 (s, 1H, H-6); 9.2 (s, 1H, H-2)
10e	44	> 300° (DMF/H_2O)	$C_{13}H_{13}N_5$ (239.2)	239 (100)	2.45 (s, 6H, $2CH_3$); 7.0–7.4 (m, 3H); 9.15 (s, 1H, H-6); 9.3 (s, 1H, H-2)
11a	44	> 300° (n-C_4H_9OH)	$C_{12}H_{10}N_4$ (210.2)	210 (100)	7.5–8.1 (m, 6H); 8.5–8.8 (m, 2H, H-5, H-7)
11b	49	> 300° (DMF)	$C_{13}H_{12}N_4$ (224.2)	224 (100)	2.5 (s, 3H, CH_3); 7.2–7.6 (A_2B_2-system, 4H); 7.85 (dd, 1H, J = 7.5 Hz, 6 Hz, H-6); 8.3–8.7 (m, 2H, H-5, H-7)
11c	40	293–295° (DMF)	$C_{13}H_{12}N_4O$ (240.2)	240 (68)	4.1 (s, 3H, OCH_3); 7.2–8.1 (m, 5H); 8.4–8.8 (m, 2H, H-5, H-7)
11d	40	278–280° (C_2H_5OH)	$C_{14}H_{14}N_4$ (238.2)	238 (100)	2.35 (s, 3H, CH_3); 2.45 (s, 3H, CH_3); 7.2–7.5 (m, 3H); 7.8 (dd, 1H, J = 7.5 Hz, 6 Hz, H-6); 8.3–8.7 (m, 2H, H-5, H-7)
11e	42	> 300° (DMF)	$C_{14}H_{14}N_4$ (238.2)	238 (100)	2.45 (s, 6H, $2CH_3$); 7.1–7.5 (m, 3H); 7.9 (dd, 1H, J = 7.5 Hz, 6 Hz, H-6); 8.4–8.8 (m, 2H, H-5, H-7)
12a	62	264–266°	$C_{12}H_{10}N_4$ (210.2)	210 (95)	6.8–8.3 (m, 9H); 8.65 (s, 1H, H-4)[c]
12b	47	230–232°[d] (C_2H_5OAc)	$C_{13}H_{12}N_4$ (224.2)	224 (100)	2.3 (s, 3H, CH_3); 7.1–8.4 (m, 8H); 8.7 (s, 1H, H-4)[c]
12c	55	298–300°[e]	$C_{14}H_{14}N_4$ (238.2)	238 (100)	2.3 (s, 6H, $2CH_3$); 6.6–8.4 (m, 7H); 8.65 (s, 1H, H-4)[c]

[a] Satisfactory microanalyses obtained: C ± 0.15, H ± 0.19, N ± 0.18.
[b] No ionization.
[c] In DMSO-d_6.
[d] Softnening from 150°C.
[e] Darkening from 290°C.

dimethylformamide (6 ml) is refluxed for 5 h. The solvent is vacuum-distilled and the crude product is treated with ether (30 ml) and isolated by suction, to give **14**, identical with a sample prepared as described elsewhere[13]; yield: 0.408 g (90%).

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